Effect of Short-term Treatment With Gaboxadol on Sleep Maintenance and Initiation in Patients With Primary Insomnia

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Study Objective: To perform an early evaluation of the efficacy and safety of gaboxadol in the treatment of primary insomnia.

Methods: 26 adults (18-65 years) with DSM-IV criteria for primary insomnia were randomly assigned gaboxadol (5mg, 15mg) or placebo in a double-blind, crossover study. After a 3-night polysomnographic (PSG) screen, treatment was administered 30 min before bedtime on 2 consecutive nights during 3 separate sessions including PSG. Efficacy analyses (n=23) were based on the average of Nights 1 and 2, and compared gaboxadol versus placebo. Baseline was the average of Nights 2 and 3 of the screening session. Both gaboxadol doses significantly ($P < 0.05$) improved mean total sleep time (mean ± SD: baseline = 368.0 ± 51.1 min, 15 mg = 420.3 ± 24.5 min, 5 mg = 419.8 ± 20.4 min, placebo = 408.7 ± 30.4 min). Both gaboxadol doses reduced mean wake after sleep onset, although statistical significance was only achieved with 5 mg (baseline = 61.6 ± 35.4 min, 15 mg = 38.0 ± 21.1 min, 5 mg = 34.6 ± 14.3 min, placebo = 43.4 ± 22.9 min). Gaboxadol 15 mg also significantly reduced mean latency to persistent sleep (baseline = 55.6 ± 27.0 min, 15 mg = 23.6 ± 15.1 min, placebo = 30.0 ± 19.1 min) and enhanced slow wave duration (baseline = 72.4 ± 20.8 min, 15 mg = 114.0 ± 37.5 min, placebo = 93.9 ± 31.3 min) with no significant effects on REM sleep duration. Patient reports (Leeds Sleep Evaluation Questionnaire) of reduced time to sleep and increased sleep quality showed significant improvement with gaboxadol 15 mg. No next-day residual effects were observed with either dose of gaboxadol (assessed 2 h and 9 h after lights on). All adverse events were mild or moderate.

Conclusion: Gaboxadol 15 mg was effective and generally well tolerated in the short-term treatment of patients with primary insomnia. Gaboxadol also enhanced slow wave sleep duration and had no significant effects on REM sleep duration. These findings suggest that gaboxadol may be a useful treatment for insomnia.

Keywords: Gaboxadol, primary insomnia, polysomnography, sleep, slow wave sleep, GABA, selective extrasynaptic $GABA_A$ agonist, SEGA, sleep quality, sleep latency, sleep maintenance

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INTRODUCTION

TREATMENT STRATEGIES FOR INSOMNIA SHOULD IDEALLY ALLEVIATE THE NOCTURNAL SYMPTOMS, IMPROVE THE FEELING OF NONRESTORATIVE SLEEP, AND reduce the impairment of daytime function that patients report in this often chronic condition. Current pharmacological approaches center primarily on activity at the benzodiazepine receptor binding site of the gamma amino butyric acid (GABA) subtype A ($GABA_A$) receptor. GABA is the major inhibitory neurotransmitter in the central nervous system, and both classical benzodiazepines such as triazolam and nonbenzodiazepines such as zolpidem act similarly as modulators of GABA at the benzodiazepine binding site. These traditional hypnotics tend to facilitate the occurrence of shallow sleep (e.g., stage 2) and, to varying degrees, suppress rapid eye movement (REM) sleep while either having no effects on, or suppressing, slow wave sleep (SWS, stages 3 and 4) and slow wave activity (SWA) as measured with power spectral analysis.[1-5] Furthermore, for some of these agents, problems may arise either during or after the course of treatment due to next-day residual effects (hangover), development of tolerance and dependence, or rebound insomnia.[6-8]

The greater receptor selectivity and improved pharmacokinetic profile of the nonbenzodiazepines compared with the classical benzodiazepines have yielded clinically important benefits. However, tolerability concerns have been raised even with the newer medications, particularly with respect to residual and amnestic effects.[9,10] A recent meta-analysis of the risks and benefits of sedatives in the elderly found similar cognitive adverse event profiles with classical benzodiazepines and nonbenzodiazepine drugs (zaleplon, zolpidem, and zopiclone).[11] In addition, the abuse liability of some of these compounds, particularly that of zaleplon, zopiclone, and eszopiclone, has been suggested to be similar to that of benzodiazepines such as temazepam and triazolam.[12] There is thus interest in developing compounds that target different receptors that may have more specific effects on the regulation of sleep without these and other side effects.

Gaboxadol is a novel selective extrasynaptic $GABA_A$ agonist (SEGA), currently in clinical development for the treatment of insomnia.[13] The $GABA_A$ receptor is a pentameric transmembrane protein consisting of 5 subunits that form a central anion channel. Gaboxadol binds at the interface between the α and β subunits, the same site utilized by the endogenous GABA ligand. Gabox-

Disclosure Statement

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adol is thus able to exert direct effects on chloride conductance, independent of GABA. The mechanism of action of gaboxadol is unique in that it directly activates extrasynaptically located δ-containing receptors via interaction with the GABA binding site.[14-17] The extrasynaptic δ-containing receptors are predominantly expressed in the thalamus, cerebral cortex, and limbic system; these brain regions have been implicated in sleep regulation and synchronization of cortical activity.[18-20] In contrast, benzodiazepine-site ligands such as traditional benzodiazepines (e.g., triazolam) and nonbenzodiazepines (e.g., zolpidem) primarily and allosterically modulate synaptically located $\alpha_1\beta\gamma_2$-containing receptors via interaction with the benzodiazepine binding site (i.e., these agents act by amplifying the response to GABA binding at the receptor) and do not activate δ-containing $GABA_A$ receptor subunits.[21] When given orally in healthy subjects, gaboxadol is rapidly absorbed (t_{max} of 30-60 min) and eliminated (t½ of 1.5 h). More than 95% of the dose is excreted in the urine, mostly unchanged. A glucoronide conjugate is the only metabolite formed in significant amounts. Hence the CYP450 system does not have significant involvement in the metabolism of gaboxadol.

It is known from studies in healthy young and elderly subjects, as well as studies in animals, that gaboxadol increases NREM sleep, sleep continuity, enhances delta activity within NREM sleep, and increases SWS/SWA without suppressing REM sleep.[22-28] These observations suggest that gaboxadol might have therapeutic potential in the treatment of insomnia and might offer some benefits over existing treatments. The objective of the present early-phase clinical trial was to explore the short-term efficacy and safety of gaboxadol after 2 nights of treatment in patients with primary insomnia. This is the first evaluation of the clinical profile of gaboxadol to be reported in patients with primary insomnia.

METHODS

Design

This was an exploratory, randomized, double-blind, 3-way crossover, sleep laboratory polysomography (PSG) study designed to compare the effects of gaboxadol 5 mg and 15 mg versus placebo on: 1) traditional hypnotic PSG efficacy measures, 2) sleep architecture, 3) subjective sleep, and 4) safety and tolerability. The study was conducted at a single investigative site (FORENAP - Institute For Research in Neurosciences, Neuropharmacology and Psychiatry, Centre Hospitalier, Rouffach, France). The Lundbeck study number was 99564.

Patients

Patients with primary insomnia aged 18–65 years were enrolled based on the DSM-IV criteria for primary insomnia.[29] Patients had continuous complaints of sleep difficulties for the last month or longer, a score >5 on the Pittsburgh Sleep Quality Index[30] and met the following criteria during a 3-night PSG screening session: A) latency to persistent sleep ≥30 min on Night 2 or 3 and not <20 min on the other night (Night 2 or 3), B) total sleep time <420 min on Night 2 or 3 and not >430 min on the other night, C) wakefulness during sleep >48 min or >10 night awakenings on Nights 2 and 3.

Patients were not eligible if they had been taking any of the following medications prior to the screening visit: within 2 weeks - triazolam, zolpidem, zopiclone, or zaleplon; within 4 weeks - other benzodiazepines, anticholinergics, anti-epileptic drugs, antihistamines, centrally-acting antihypertensives, sympathicomimetics, or psychotropics; within 3 months - fluoxetine. Patients were also excluded at screening if they: A) had been treated with >5 different hypnotics, of at least 2 weeks treatment duration, during the last year (hypnotic-resistant patients); B) consumed >3 alcohol containing beverages or >5 caffeine containing beverages daily; C) had a positive result at screening for alcohol and/or drug of abuse (opiates, methadone, cocaine, amphetamine, ecstasy, cannabinoid, benzodiazepines, zolpidem, zopiclone, barbiturates, and anti-histamines); D) had a history of alcohol or drug abuse as defined in DSM-IV; or E) had any clinically significant disease such as liver or renal insufficiency, cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, infectious, neoplastic, or metabolic disturbance.

Patients were recruited when presenting with insomnia complaints at one of the authors' clinics, and by newspaper advertisements and flyers in letterboxes. They were paid for their inconvenience and travel expenses incurred participating in the study. All patients gave written informed consent, and the study (including patient payments) was approved by the ethics committee, Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Strasbourg.

PROCEDURE

Patients attended a medical screening visit during which their demographic data, medical, psychiatric, and medication histories and symptoms of primary insomnia according to the DSM-IV criteria[29] were recorded. Selection interviews were initially performed by a trained clinical psychologist with experience in cognitive-behavioral therapy of insomniac patients. Vital signs, electrocardiogram, blood biochemistry, haematology, and a urine analysis were carried out at screening visit. Standard daytime EEG was conducted at screening to exclude patients with EEG abnormalities (e.g., unknown epilepsy, unknown brain metastasis). Medical reviews and physical, neurological, and psychiatric examinations were performed by a physician.

Patients who satisfied eligibility criteria attended the sleep laboratory for a screening session consisting of 3 nights of PSG recording lasting from 23:00 to 07:00. Patients were not maintained on a prelaboratory sleep/wake schedule or required to keep a sleep diary but were interviewed at screening to ensure they met usual bedtime hours between 22:00-00:00 to 06:00-08:00. Specific PSG exclusion criteria for periodic limb movement syndrome were an arousal index >10/hour, and for sleep apnea syndrome, an apnea-hypopnea index >5/h. PSG inclusion/exclusion criteria were evaluated by a physician specialized in sleep medicine. The PSG entry criteria were also reviewed by an independent sleep scoring laboratory before the patient could be included into the study. Those patients who met the PSG eligibility criteria then entered the randomized, double-blind, crossover treatment phase of the study. Patients were randomly assigned to 1 of 6 treatment sequences according to a Williams Latin square design in which every treatment followed every other treatment once. The randomization code was generated independently from the study site. The treatments (gaboxadol 5 mg, gaboxadol 15 mg, and placebo) were encapsulated to ensure study blinding. Patients were administered the allocated treatment 30 min before bedtime (and lights off) at 23:00 on 2 consecutive nights during 3 separate

PSG sessions, each separated by a washout period of 7-14 days. PSG was recorded from 23:00h to 07:00 on each of the 2 nights per session. The patients' own evaluation of their sleep was recorded the morning after each treatment, 30 min after awakening (lights on 07:00), using the Leeds Sleep Evaluation Questionnaire (LSEQ).[31] Next-day residual effects were evaluated using a selection of tests from the Cognitive Drug Research (CDR) test battery (CDR Ltd, Reading, UK) at 09:00 and 16:00 the day after each drug administration. Patients performed 4 practice sessions on the CDR test battery on the day after the 3rd PSG screening night. All patients returned for a follow-up visit 7-14 days after the final PSG session. Adverse events were recorded throughout the study and were rated by the investigator with regard to severity and likelihood of being drug-related. Vital signs, electrocardiogram, routine laboratory assessments, and physical examinations were performed at regular intervals. During evaluation days, patients remained in the study centre during the entire period. Breakfast was at 08:00 and lunch at 12:30. Exercise and intake of caffeine and alcohol were prohibited, and patients were not allowed to go to bed or take a nap during the daytime. No smoking was allowed in the centre, but smoking was allowed outside the sleep centre under supervision of a nurse. Smoking was not possible within 1 h of bedtime on PSG nights.

Assessments

Visual scoring of PSG data was performed by blinded personnel in 30-sec epochs according to the criteria described by Rechtschaffen & Kales.[32] Visually scored measures of hypnotic efficacy included: latency to persistent sleep (LPS) defined as the time from lights out to the beginning of 10 consecutive minutes of stage 2, 3, 4 or REM sleep; total sleep time (TST) defined as REM + NREM sleep times excluding movement time; total time awake (TTA) defined as the total amount of time spent awake during time in bed; number of awakenings (NAW) defined as the number of times from sleep onset that at least one wake epoch occurred separated by at least one nonwake epoch; wake after sleep onset (WASO) defined as the total amount of time spent awake from the start of 20 consecutive epochs of stage 1-4 or REM sleep to lights on; and sleep efficiency defined as 100*TST/time in bed. Effects on sleep architecture were evaluated by measuring the duration of each sleep stage including latency to REM sleep.

Self-reported measures of sleep were evaluated using the LSEQ.[31] This questionnaire consists of ten 100-mm visual analogue scales pertaining to 4 aspects of sleep: 1) getting to sleep, 2) quality of sleep, 3) awakening from sleep, 4) behaviour following wakefulness. A score of 100 mm indicates the largest possible positive change experienced after drug administration. Conversely, 0 mm indicates the largest possible negative change experienced after drug administration.

To assess next-day residual effects a selection of tasks from the CDR computerized cognitive assessment system were chosen to assess a range of cognitive functions including attention, working memory, long-term memory, and skilled motor co-ordination (CDR Ltd, Reading, UK). Assessments were performed at 09:00 (2 h after lights on) and 16:00 (9 h after lights on) on both days following treatment the night before. The battery consisted of tests of simple reaction time (speed in msec), choice reaction time (speed in msec), digit vigilance (speed of detection in msec, % of targets detected), visual tracking (average distance from target in mm), spatial working memory (sensitive index, speed in msec), digit symbol substitution test (number correct), picture recognition (sensitivity index, speed in msec) and critical flicker fusion (threshold in Hz). Most tasks were computer controlled on high resolution screens with the responses recorded via a response module containing 2 buttons, one marked "NO" and the other "YES." In addition, the tracking task involved the use of a joystick, and the critical flicker fusion task involved the use of a light box. A paper test sheet was used for the digit symbol substitution test. The tests were administered in the following order - picture presentation, simple reaction time, digit vigilance, choice reaction time, tracking, spatial working memory, digit symbol substitution, picture recognition and critical flicker fusion threshold.

Data Analysis

Efficacy analyses (PSG and LSEQ) were performed on the per-protocol set (PPS) as described in a predefined analysis plan. The PPS consisted of all randomized patients who received active treatment up to and including the second treatment night of the third treatment session and who did not violate any of the inclusion or exclusion criteria. The PSG and LSEQ efficacy data were averaged for nights 1 and 2. The last 2 nights of the screening session served as the baseline. The data were analyzed using the SAS® version 8 statistical software package. The analysis was based on an analysis of covariance with fixed effects for treatment, sessions, and sequence, and with a random effect of patients within sequence. When ANCOVA revealed a significant main effect of treatment, planned contrasts were performed between placebo and each active dose. Sample size determination was made for comparison of an active drug condition versus placebo on PSG LPS (and not between active doses). No correction for multiple comparisons was used for PSG and LSEQ variables, since the study was designed primarily to find one or more doses of gaboxadol which differed from placebo on a small number of PSG measures (LPS and TST). The remainder of the statistical comparisons are exploratory. Analysis results related to these variables were intended to help characterize patients' responses to gaboxadol compared with placebo; therefore no multiplicity adjustment was used for these analyses (nominal P-values are presented). Data were assessed for normality and, if appropriate, a logarithmic transform was applied. Standardized effect sizes have also been estimated relative to placebo and are presented where relevant. The average of nights 2 and 3 of the PSG screening session was used as baseline. The study was designed to provide adequate lengths of washout periods to avoid potential carryover effects. The lack of carryover effects was confirmed from exploratory statistical analyses by period and analyses of potential sequence and treatment by period interactions.

Analyses of routine safety measures (e.g., adverse events, laboratory values) were performed on the all-patients-treated set defined as all randomized patients who took at least 1 dose of double blind study medication. Descriptive summary statistics were calculated for these assessments. The analysis of the CDR test battery was based on the set of randomized patients who took at least 1 dose of study treatment and who had at least one post-baseline assessment. The SAS® PROC MIXED procedure was used to conduct analysis of variance at each time point fitting dosing condition as a fixed factor and patient as a random factor (i.e., the data were not combined across assessment days, or

Table 1—Sleep maintenance and induction parameters derived from visual scoring of PSG data at baseline and following treatment

Parameter (mean ± SD)	Baseline[b] (N=23)	Placebo[c] (N=23)	Gaboxadol 5 mg[c] (N=23)	Gaboxadol 15 mg[c] (N=23)
TST (min)	368.4 ± 51.1	408.7 ± 30.4	419.8 ± 20.4*	420.3 ± 24.5**
TTA (min)	109.6 ± 48.0	68.5 ± 30.8	58.2 ± 21.0*	57.3 ± 25.0*
WASO (min)[a]	61.6 ± 35.4	43.4 ± 22.9	34.6 ± 14.3*	38.0 ± 21.1
NAW (n)	27.0 ± 8.8	23.2 ± 9.4	23.5 ± 9.0	22.6 ± 10.4
SEI (% time asleep in bed)	76.5 ± 10.0	85.2 ± 6.3	87.5 ± 4.3*	87.7 ± 5.1**
LPS (min)[a]	55.6 ± 27.0	30.0 ± 19.1	28.3 ± 15.8	23.6 ± 15.1*

TST total sleep time; TTA total time awake; WASO wake after sleep onset; NAW number of awakenings; SEI sleep efficiency index; LPS latency to persistent sleep.

[a] P-values are based on log-transformed data

[b] average of nights 2 and 3 of the screening session

[c] average of nights 1 and 2 of the treatment session

*P <0.05 versus placebo, **P <0.01 versus placebo

across assessment times within each day). The SAS® LS MEANS procedure was used to make contrasts between placebo and each active dose.

RESULTS

Patient Accounting and Baseline Characteristics

A total of 113 patients were screened in order to randomize 26 patients. The main reason for ineligibility during screening was the PSG sleep onset entry criterion where 31 (27%) of the screened patients were excluded. Other reasons for exclusion were abnormal biology (n=15, 13%), sleep apnea (n=9, 8%), PLMD (n=7, 6%), abnormal medical/psychiatric/neurological history (n=7, 6%), other sleep related problems/disorders (n=5, 4%), drugs of abuse (n=4; 4%), personal reasons (n=4, 4%), current sleeping medications (n=3, 3%), WASO entry criteria (n=1, 1%) and other (n=1, 1%). The 26 randomized patients all received at least one dose of double-blind medication and were included in the all-patients-treated set used for the analysis of routine safety measures. (All 26 randomized patients also had a least 1 post-baseline assessment and were therefore included in the analysis of the CDR measures). These 26 patients consisted of 19 women and 7 men with a mean age of 34.6 years (SD 10.8), mean body mass index of 23.6 kg/m^2 (SD 4.1) and mean Pittsburgh Sleep Quality Inventory score of 11.2 (SD 2.3). Among the 26 patients randomized, 3 protocol violators were excluded from the PPS (n=23) used for the efficacy analysis. Two patients were excluded immediately after randomization because of abnormal laboratory test results unrelated to study treatment and one patient violated the PSG entry criteria for NAW/WASO but completed the study.

Efficacy

The effects of gaboxadol on sleep maintenance and onset measures are presented in Table 1. Both gaboxadol doses improved TST (by about 52 min versus baseline and 11 min versus placebo with a standardized effect size of 0.43 for 5 mg and 0.42 for 15 mg versus placebo) and sleep efficiency (by about 11 percentage points versus baseline and 2.5 percentage points versus placebo, with a standardized effect size of 0.43 for 5 mg and 0.44 for 15 mg versus placebo) and reduced the TTA (by about 53 min versus baseline and 10-11 min versus placebo with a standardized effect size of 0.39 for 5mg and 0.40 for 15mg versus placebo). Both gaboxadol doses reduced WASO (by about 24-27 min versus baseline and 5-8 min versus placebo) but statistical significance was achieved only with the 5 mg dose (standardized effect size of 0.46). When looking at the individual nights separately, both gaboxadol doses significantly reduced WASO on Night 1 (mean ± SD: 15 mg = 35.6 ± 18.0 min, 5 mg = 32.6 ± 15.9 min, placebo = 48.4 ± 28.6 min) but not on Night 2 (15 mg = 40.3 ± 26.7 min, 5 mg = 36.7 ± 17.2 min, placebo 38.4 ± 20.7 min), suggesting that the lack of significant findings in the combined night WASO analysis for gaboxadol 15 mg may have been a consequence of the greater variance seen with this dose. No treatment effects were observed with regard to NAW. There was no clear dose response effect on any sleep maintenance parameter. With regard to sleep onset, gaboxadol 15 mg improved LPS by about 32 min versus baseline and 6 min versus placebo (standardized effect size of 0.37). The 5 mg dose did not have a significant effect on LPS.

Effects of gaboxadol on sleep architecture are presented in Table 2. Neither gaboxadol dose significantly affected REM duration or latency compared with placebo. A numeric reduction in REM duration was observed for gaboxadol 15 mg versus placebo, but these data are difficult to interpret since gaboxadol 15 mg increased REM duration relative to baseline. No change was observed in the duration of stage 1 or stage 2 sleep, whereas SWS duration (sum of stages 3 and 4) was strongly enhanced by the 15 mg dose (by 20 min) compared with placebo (P <0.001). This was due to enhancement of both stage 3 and stage 4 sleep (both P <0.001).

In terms of subjective evaluation of sleep and next day feeling/behaviour assessed by the LSEQ, gaboxadol 15 mg significantly improved “getting to sleep” (P = 0.034, standardized effect size of 0.60) and “quality of sleep” (P = 0.022, standardized effect size of 0.61) without any deleterious effect on the “awakening from sleep” and “behavior following sleep” compared with placebo (Table 3). Gaboxadol 5 mg had no effect on any LSEQ parameter.

Safety

Both doses of gaboxadol were generally well tolerated, and all adverse events were mild or moderate in severity (Table 4). There were no clinically important significant changes from baseline in

Table 2—Sleep architecture parameters derived from visual scoring of PSG data at baseline and following treatment

Parameter (mean ± SD)	**Baseline[b] (N=23)**	**Placebo[c] (N=23)**	**Gaboxadol 5 mg[c] (N=23)**	**Gaboxadol 15 mg[c] (N=23)**
Stage 1 duration (min)[a]	22.0 ± 11.3	17.0 ± 6.4	18.1 ± 7.4	17.0 ± 7.5
Stage 2 duration (min)	193.3 ± 31.5	205.1 ± 39.0	210.8 ± 35.1	204.6 ± 36.5
Stage 3 duration (min)	16.6 ± 5.7	19.1 ± 10.1	20.6 ± 8.6	25.8 ± 11.9***
Stage 4 duration (min)	55.8± 19.6	74.7 ± 25.0	74.6 ± 30.5	87.8 ± 28.5***
SWS duration (min)	72.4 ± 20.8	93.9 ± 31.3	95.3 ± 36.9	114.0 ± 37.5***
REM duration (min)	79.4 ± 19.7	92.7 ± 21.6	95.6 ± 19.1	85.2 ± 22.2
REM latency (min)	77.6 ± 30.4	68.4 ± 20.8	61.4 ± 20.0	70.2 ± 19.7

[a] P-values are based on log-transformed data
[b] average of nights 2 and 3 of the screening session
[c] average of nights 1 and 2 of the treatment session
***$P < 0.001$ versus placebo

Table 3—Subjective sleep assessment by LSEQ following treatment

Parameter[a] (mean ± SD)	**Placebo[b] (N=22)**	**Gaboxadol 5 mg[b] (N=22)**	**Gaboxadol 15 mg[b] (N=22)**
Quality of sleep (mm)	51.4 ± 10.0	48.2 ± 14.2	59.7 ± 16.4*
Getting to sleep (mm)	50.2 ± 12.6	51.3 ± 11.0	58.5 ± 14.8*
Awakening from sleep (mm)	49.5 ± 13.2	47.6 ± 11.6	52.5 ± 17.3
Behavior following wakefulness (mm)	50.5 ± 15.4	47.6 ± 14.2	49.8 ± 12.7

[a] A score of 100 mm indicates the largest possible positive change experienced after drug administration. Conversely, 0 mm indicates the largest possible negative change experienced after drug administration.
[b] average of nights 2 and 3 of the treatment session
*$P < 0.05$ versus placebo

Table 4—Summary of adverse events, regardless of relationship to treatment

Number (%) of patients	**Placebo (N=24)**	**Gaboxadol 5 mg (N=26)**	**Gaboxadol 15 mg (N=25)**
Total patients with ≥1 adverse event	8 (33%)	10 (38%)	7 (28%)
Abdominal pain	3 (13%)	1 (4%)	2 (8%)
Insomnia	1 (4%)	1 (4%)	1 (4%)
Somnolence (daytime)	2 (8%)	0	3 (12%)
Dizziness	0	0	2 (8%)
Fatigue	1 (4%)	1 (4%)	0
Headache	2 (8%)	1 (4%)	0
Thinking abnormal	1 (4%)	0	1 (4%)
Asthenia	0	1 (4%)	0
Depression	0	0	1 (4%)
Diarrhea	0	1 (4%)	0
Hepatic enzymes increased	0	1 (4%)	0
Fungal infection	0	1 (4%)	0
Influenza-like symptoms	0	1 (4%)	0
Migraine	0	1 (4%)	0
Nausea	0	0	1 (4%)
Pharyngitis	1 (4%)	0	0
Rash	0	1 (4%)	0
Syncope	0	0	1 (4%)
Tooth disorder	0	0	1 (4%)

biochemistry, haematology, urinalysis, vital signs, or electrocardiogram values. No noteworthy changes were observed on physical or neurological clinical examinations.

Mean scores on the CDR battery at the 09:00 time point on Day 2 are shown in Table 5. Of the time points assessed, this was the one thought most likely to show evidence of any adverse cognitive effects. There were no significant findings, suggesting that neither dose of gaboxadol impaired next day cognitive function. Similar findings were apparent at the 16:00 time point on day 2 and at the 09:00 and 16:00 evaluations on Day 3 (data not shown). The only measure which showed a significant main effect of dosing condition in the analysis of variance was digit vigilance speed at the 16:00 time point on Day 2 ($P = 0.021$); the treatment comparisons indicated a significantly shorter response time for gaboxadol 15 mg over placebo by approximately 14 msec ($P = 0.007$). There were no period effects seen with these tests suggesting no significant learning effect during the treatment periods.

DISCUSSION

In this early-phase exploratory study, short-term treatment with gaboxadol 15 mg over 2 nights improved both sleep maintenance and sleep onset PSG efficacy measures. These objective improvements were supported by improvements in the patients' subjective ratings with regard to their ease in getting to sleep (i.e., sleep latency) and their sleep quality. The improvements in subjective sleep were not accompanied by a subjective deterioration in awakening from sleep or behavior such as clumsiness following sleep. The 5 mg dose of gaboxadol had some beneficial effects on sleep maintenance, and there was no clear dose-response relationship with regard to this aspect of hypnotic efficacy. However, unlike the 15 mg dose, the 5 mg dose had no effect on objective or subjective measures of sleep onset.

The size of the benefits observed with gaboxadol appeared modest in some cases. However, it is difficult to extrapolate the direct clinical relevance of the findings from this relatively limited dataset. It is noteworthy that significant effects of gaboxadol 15 mg on sleep maintenance and onset were found despite a relatively large placebo response. The large placebo response may have been influenced by the lack of a placebo run-in period, which has been used in some recent trials in order to exclude patients with an excessive placebo response. The large placebo

Table 5—Next-day residual effects assessed by the CDR Test Battery at 09:00 on Day 2

Measure (Mean ± SE)	Placebo (N=24)	Gaboxadol 5 mg (N=26)	Gaboxadol 15 mg (N=25)
Simple reaction time (msec)	272.9 ± 9.6	270.1 ± 9.3	266.0 ± 10.7
Choice reaction time (msec)	492.2 ± 15.1	481.6 ± 13.1	469.9 ± 15.9
Digit vigilance (speed, msec)	412.6 ± 9.0	411.3 ± 8.5	411.9 ± 11.4
Digit vigilance (% targets detected)	96.6 ± 0.7	96.2 ± 1.0	96.8 ± 0.9
Visual tracking (average distance from target, mm)	32.4 ± 2.6	34.1 ± 3.4	31.2 ± 1.8
Spatial working memory (sensitivity index)	0.92 ± 0.02	0.85 ± 0.05	0.94 ± 0.02
Spatial working memory (speed, msec)	778.1 ± 49.1	786.8 ± 62.6	763.6 ± 43.6
Digit symbol substitution (number correct)	42.6 ± 1.4	41.9 ± 1.5	42.4 ± 1.3
Picture recognition (sensitivity index)	0.82 ± 0.04	0.81 ± 0.03	0.84 ± 0.02
Picture recognition (speed, msec)	885.8 ± 38.1	882.2 ± 36.8	856.2 ± 36.5
Critical flicker fusion (threshold, Hz)	40.2 ± 1.0	41.3 ± 1.1	42.6 ± 1.4

response may have partly contributed to the variable efficacy of gaboxadol 15 mg over the different sleep maintenance measures. Gaboxadol 15 mg improved TST and sleep efficiency and reduced TTA, compared with placebo. A statistically significant reduction in WASO was not achieved with gaboxadol 15 mg in the combined nights analysis, probably due to the increased variance compared with the 5 mg dose; both doses were significantly superior to placebo when looking at Night 1 data only. Conceivably, the increased variance may be because some patients accommodated to the sleep maintenance effects of gaboxadol 15 mg from Night 1 to Night 2. There were also no clear treatment benefits on NAW. The efficacy of gaboxadol 15 mg on some measures of sleep maintenance such as TST was not simply accounted for by an improvement in sleep latency alone, since the magnitude of effect on LPS was smaller than the effect on TST. In addition to the large placebo response, the restriction of the recording period to 8 h, as well as the relatively small size of the study and short duration of treatment, may underestimate the true effects of gaboxadol on sleep maintenance.

The observation that gaboxadol improved some sleep maintenance measures is notable given its relatively short half-life of approximately 1.5 h. The mechanism for gaboxadol's effects on sleep maintenance is unclear. Selection of current sleep aids by physicians typically involves a tradeoff whereby an extended effect on sleep maintenance to carry patients through the night requires a treatment with a long half-life and an associated risk of residual effects extending into the next day.[8] Thus, drugs with short half-lives such as zaleplon (t½ of 1 h) appear to improve sleep latency with limited benefits on sleep maintenance and are considered most appropriate for treating sleep onset insomnia, while drugs with longer half-lives such as zopiclone and eszopiclone (t½ of 7 h) may be considered more appropriate where patients also have sleep maintenance difficulties but with risk of hangover effects. The present findings suggest that gaboxadol may have potential as a treatment which improves both sleep maintenance and onset without the residual side effects of longer half-life agents.

The results from the present study confirmed findings in previous studies in healthy subjects and animals, indicating that gaboxadol has a distinct profile of effects on sleep architecture.[22-28] Previous studies have demonstrated that classical benzodiazepines prolong stage 2 sleep and reduce both SWS and REM sleep, whereas nonbenzodiazepines seem to exert little, if any, effect on visually scored sleep architecture parameters.[2] Based on the visual scoring of the PSG data, SWS duration was strongly enhanced by gaboxadol 15 mg without any significant effects on duration of stage 1, stage 2, or REM sleep. By contrast, gaboxadol 5 mg had few effects on sleep architecture. It is not clear at present whether enhancing SWS translates into clinical benefits for treating insomnia. Beyond hypnotic effects per se, there has been speculation that SWS may be involved in learning and memory processes. Overnight improvements in (both perceptual and motor) procedural memory function may be linked to some degree with the underlying physiology manifest in SWS.[33-35] Improvement in spatial learning (declarative) memory may also be dependent upon processes underlying SWS.[36] The ability of gaboxadol to enhance SWS may provide a useful pharmacological probe to help elucidate the role of SWS (and sleep architecture in general) in learning and memory.

In terms of its safety profile, short-term use of gaboxadol was generally well tolerated at both 5 mg and 15 mg doses. All adverse events were mild or moderate in severity. The results from the CDR test battery suggested that gaboxadol does not produce any residual hangover effects at the doses investigated. The lack of residual effects is consistent with preclinical data suggesting that gaboxadol is functionally inactive at central nervous system receptor sites associated with adverse effects on memory and cognition.[17]

In conclusion, the present data showed that short-term treatment with gaboxadol 15 mg to some degree improved sleep maintenance and onset in patients with primary insomnia. The treatment was generally well tolerated. The previously observed increase in SWS in healthy subjects was confirmed in primary insomnia patients. Further studies are required to elucidate the clinical benefits, if any, of enhancing SWS. These initial efficacy and safety findings require extrapolation in larger and longer-term trials in order to determine the true clinical relevance, but suggest that gaboxadol may be a useful treatment for insomnia.

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Abbreviations

CDR	Cognitive Drug Research
DSM-IV	Diagnostic and statistical manual of mental disorders version IV
GABA	gamma amino butyric acid
GABA$_A$	gamma amino butyric acid,subtype A
LPS	Latency to persistent sleep
LSEQ	Leeds Sleep Evaluation Questionnaire
NAW	Number of wakenings
NREM	Non rapid eye movement
PPS	Per-protocol data set
PSG	Polysomography
REM	Rapid eye movement
SD	Standard deviation
SE	Standard error
SEGA	Selective extrasynaptic GABA$_A$ agonist
SEI	Sleep efficiency index
SWA	Slow wave activity
SWS	Slow wave sleep
TST	Total sleep time
TTA	Total time awake
WASO	Wake after sleep onset

REFERENCES

1. Parrino L, Terzano MG. Polysomnographic effects of hypnotic drugs. A review. Psychopharmacology (Berl) 1996;126:1-16.
2. Mitler MM. Nonselective and selective benzodiazepine receptor agonists--where are we today? Sleep 2000;23 Suppl 1:S39-47.
3. Feinberg I, Maloney T, Campbell IG. Effects of hypnotics on the sleep EEG of healthy young adults: new data and psychopharmacologic implications. J Psychiatr Res 2000;34:423-38.
4. Brunner DP, Dijk DJ, Munch M, Borbely AA. Effect of zolpidem on sleep and sleep EEG spectra in healthy young men. Psychopharmacology (Berl) 1991;104:1-5.
5. Trachsel L, Dijk DJ, Brunner DP, Klene C, Borbely AA. Effect of zopiclone and midazolam on sleep and EEG spectra in a phase-advanced sleep schedule. Neuropsychopharmacology 1990;3:11-8.
6. Petursson H. The benzodiazepine withdrawal syndrome. Addiction 1994;89:1455-9.
7. Vermeeren A. Residual effects of hypnotics: epidemiology and clinical implications. CNS Drugs 2004;18:297-328.
8. Sateia MJ, Nowell PD. Insomnia. Lancet 2004;364:1959-73.
9. Hindmarch I, Patat A, Stanley N, Paty I, Rigney U. Residual effects of zaleplon and zolpidem following middle of the night administration five hours to one hour before awakening. Hum Psychopharmacol 2001;16:159-67.
10. Roehrs T, Merlotti L, Zorick F, Roth T. Sedative, memory and performance effects of hypnotics. Psychopharmacology (Berl)1994;116:130-4.
11. Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 2005;331:1169-73.
12. Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds. J Clin Psychiatry 2005;66:31-41.
13. Wafford KA, Ebert B. Gaboxadol — a new awakening in sleep. Curr Opin Pharmacol 2006;6:30-6.
14. Belelli D, Peden DR, Rosahl TW, Wafford KA, Lambert JJ. Extrasynaptic GABA(A) receptors of thalamocortical neurons: a molecular target for hypnotics. J Neurosci 2005;25:11513-20.
15. Drasbek K, Jensen K. THIP, a hypnotic and antinociceptive drug, enhances an extrasynaptic GABAA receptor mediated conductance in mouse neocortex. Cereb Cortex 2005 Oct 12; Epub ahead of print
16. Jia F, Pignataro L, Schofield CM, Yue M, Harrison NL, Goldstein PA. An extrasynaptic GABAA receptor mediates tonic inhibition in thalamic VB neurons. J Neurophysiol 2005;94:4491-501.
17. Storustovu S, Ebert B. Pharmacological characterisation of agonists at δ containing GABAA receptors: functional selectivity for extrasynaptic receptors is dependent on absence of γ2. J Pharmacol Exp Ther 2006;316:1351-9.
18. Steriade M, McCormick DA, Sejnowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. Science 1993;262:679-85.
19. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005;437:1257-63.
20. Saper CB, Cano G, Scammell TE. Homeostatic, circadian and emotional regulation of sleep. J Comp Neurol 2005;493:92-8.
21. Sigel E. Mapping of the benzodiazepine recognition site on GABA-A receptors. Curr Top Med Chem 2005;2:833-9.
22. Lancel M, Faulhaber J. The GABAA agonist THIP (gaboxadol) increases non-REM sleep and enhances delta activity in the rat. Neuroreport 1996;7:2241-5.
23. Lancel M. The GABA(A) agonist THIP increases non-REM sleep and enhances non-REM sleep-specific delta activity in the rat during the dark period. Sleep 1997;20:1099-104.
24. Faulhaber J, Steiger A, Lancel M. The GABAA agonist THIP produces slow wave sleep and reduces spindling activity in NREM sleep in humans. Psychopharmacology (Berl) 1997;130:285-91.
25. Lancel M. Role of GABAA receptors in the regulation of sleep: initial sleep responses to peripherally administered modulators and agonists. Sleep 1999;22:33-42.
26. Lancel M, Wetter TC, Steiger A, Mathias S. Effect of the GABAA agonist gaboxadol on nocturnal sleep and hormone secretion in healthy elderly subjects. Am J Physiol Endocrinol Metab 2001;281: E130-7.
27. Mathias S, Steiger A, Lancel M. The GABA(A) agonist gaboxadol improves the quality of post-nap sleep. Psychopharmacology (Berl) 2001;157:299-304.
28. Mathias S, Zihl J, Steiger A, Lancel M. Effect of repeated gaboxadol administration on night sleep and next-day performance in healthy elderly subjects. Neuropsychopharmacology 2005;30:833-41.
29. American Psychiatric Association.Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed. Washington, DC: American Psychiatric Association; 2000.
30. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index - a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.
31. Parrott AC, Hindmarch I. The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations - a review. Psychopharmacology (Berl) 1980;71:173-79.
32. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subject. Washington DC: National Institute of Health, Publication 204. Government Printing Office. 1968.
33. Stickgold R, James L, Hobson JA. Visual discrimination learning requires sleep after training. Nat Neurosci 2000;3:1237-8.
34. Steriade M, Timofeev I. Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. Neuron 2003;37:563-76.
35. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. Nature 2004;430:78-81.
36. Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, et al. Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron 2004;44:535-45.